様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　　元 年　　６ 月 ２１ 日現在

機関番号：１５４０１
研究種目：基盤研究(C)（一般）
研究期間：2016～2018
課題番号：１６Ｋ０９３９６

研究課題名（和文）変性脂質による腫瘍性コランギオパチー発症とその制御に関する検討

研究課題名（英文）Pathogenesis and management of carcinogenic cholangiopathy induce by deteriorated lipids

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　3,400,000円

研究成果の概要（和文）：変性脂質が惹起する腫瘍性コランギオパチーにおけるペリオスチンの役割について検討した。ヒト胆管癌細胞と正常ヒト胆管上皮細胞において、変性脂質は濃度依存性・時間依存性に細胞障害とアポトーシスを惹起するとともに、ペリオスチン発現増強、SASP因子の発現増強および上皮間葉転換が惹起されることが判明し、変性脂質による胆管上皮系細胞における細胞外マトリックス発現変動、すなわちコランギオパチーは、１）SASPを介すること、２）EMT関連遺伝子およびタンパク発現増強と連動しており肝胆道系発がんとの関連が示唆された。一連の変化はインテグリン中和抗体により抑制されたことから生物製剤による治療戦略が示唆された。

研究成果の学術的意義や社会的意義
変性脂質が惹起する腫瘍性コランギオパチーにおけるペリオスチンの役割が明らかとなり、
１）SASPを介すること、２）EMT関連遺伝子およびタンパク発現増強と連動しており肝胆道系発がんとの関連が示唆されたこと、３）上記はインテグリンを介する現象であり、その中和抗体により抑制されたことから、①脂質に関する食生活習慣制御、②脂質吸収阻害薬（NPC1L1阻害薬）による治療介入、③SASP因子やインテグリンに対する生物製剤などが治療戦略として提案されることを示唆した。

研究成果の概要（英文）：Whether deteriorated lipids (DLs)induce carcinogenic cholangiopathy was studied in order to determine in part the pathogenesis and management of biliary carcinogenesis following cholangiopathy in biliary systems. As a result, DLs induced apoptosis of human bile duct cells in a dose-dependent, time-dependent manner, along with the enhanced expression of periostin and SASP factors, leading to epitherial-mesenchymal transition (EMT). These changes were cancelled by neutralized antibody for integrins, suggesting a future therapeutic strategy.

研究分野：消化器病（肝疾患・胆道疾患）、脂質代謝、動脈硬化、生活習慣病、プライマリ・ケア、内科一般

キーワード：変性脂質　EMT　ペリオスチン

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4 SASP Ib1bs8X80MSu 1)644G

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DNA 644GpK)630/ WS I

w1uS4G6Kc real-time PCR b1 Western

blot bb0/ WS 2) DNA b08(

g LPC/9-HODE H (K S DNA bisulfite K

Methylation-specific PCR DNA gb8 3)SASP Ib0o8 SASP I

(IL-8,IL-6,TGF ,CCL2,CXCL1,SA- -gal)b4G real-time PCR

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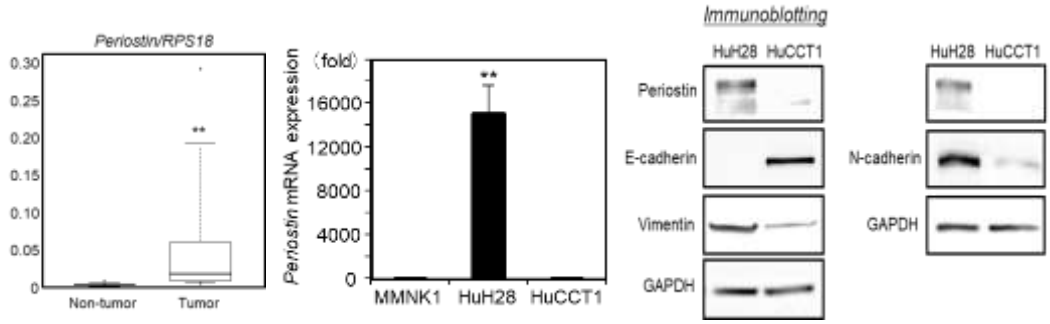

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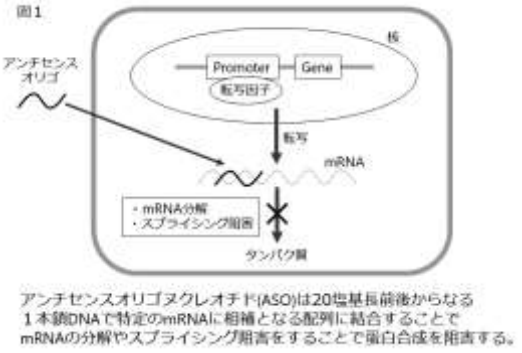

アンチセンスオリゴヌクレオチド(ASO)は20塩基長前後からなる
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mRNAの分解やスプライシング阻害をすることで蛋白合成を阻害する。

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Kanno Keishi

Kishikawa Nobusuke

Kobayashi Tomoki

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